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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Hormone treatment in gender dysphoria

Le traitement hormonal des personnes transsexuelles

El tratamiento hormonal de las personas transexuales

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KEYWORDS
Gender dysphoria;
Cross-sex hormone treatment;
Androgens;
Estrogens;
Antiandrogens

Summary In Italy hormonal treatment for persons with Gender Identity Dysphoria can be prescribed by endocrinologists only after a well-defined diagnosis has been formulated by trained psychologists/psychiatrists. Prescriptions must be preceded by exclusion of major comorbidities, which could physically and psychologically interfere with the sex reassignment procedure. Real life test is finalized to improve the psychosocial functioning according to the desired sex and allows also to confirm the diagnosis. For males who want to become women, treatment consists of estrogens and antiandrogens. For females who want to become men, treatment is most commonly composed of esters of testosterone. Venous thromboembolism, the most frequent complication in the past years, is nowadays far less frequent. The endocrinological follow-up is necessary, as postsurgical hypogonadism must be treated with chronic replacement therapy.

MOTS CLÉS
Transsexualisme ;

Résumé En Italie le traitement hormonal des personnes transsexuelles peut être prescrit par les endocrinologues seulement lorsque le diagnostic de transsexualisme est établi par des psychologues/psychiatres expérimentés. Avant que la prescription soit effectuée, il faut vérifier la présence de graves affections, ce qui pourrait compromettre au physique et au moral le parcours de changement de sexe. L'expérience de « vie réelle » se fixe le but de renforcer le rôle psychosocial selon le sexe auquel la personne transsexuelle s'identifie et permet de confirmer

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Traitement hormonal de conversion sexuelle ;
Androgènes ;
Estrogènes ;
Antiandrogènes

le diagnostic. La thérapeutique est de type estrogénique et antiandrogénique chez les hommes qui désirent devenir femme et de type androgénique, en particulier esters de testostérone, chez les femmes qui désirent devenir homme. La thrombophlébite profonde, qui était la plus sévère des complications, est plus rare aujourd'hui. Le suivi endocrinien se révèle indispensable car l'hypogonadisme conséquent à la chirurgie de transformation génitale doit être traité par le remplacement chronique des hormones appropriées.

PALABRAS CLAVE
Transexualidad;
Tratamiento hormonal de conversión sexual;
Andrógenos;
Estrógenos;
Antiandrógenos

Resumen En Italia, el tratamiento hormonal de las personas transexuales únicamente puede ser prescrito por los endocrinólogos cuando el diagnóstico de transexualidad ha sido establecido por psicólogos/psiquiatras experimentados. Antes de que se efectúe la prescripción, hay que comprobar la presencia de graves afecciones, que podrían comprometer el cambio de sexo tanto física como moralmente. La experiencia de « vida real » tiene como objetivo reforzar el papel psicosocial según el sexo con el cual se identifica el transexual y permite confirmar el diagnóstico. La terapéutica es de tipo estrogénico y anti-androgénico en los hombres que desean convertirse en mujeres y de tipo androgénico, sobre todo ésteres de testosterona, en las mujeres que desean convertirse en hombres. La tromboflebitis profunda, que representaba la complicación más severa, es menos frecuente en la actualidad. El seguimiento endocriniano es indispensable ya que el hipogonadismo consecuente a la cirugía de transformación genital debe ser tratado con una terapia de substitución hormonal crónica adecuada.

French Abridged version

La prise en charge d'adultes souffrant de troubles d'identité de genre (TIG) fait intervenir des endocrinologues qui prescrivent des traitements hormonaux (TH) destinés à modifier l'aspect physique des patients et de le faire correspondre à l'identité de genre (IG) que ces personnes revendiquent.

Les points clés universellement acceptés du traitement TIG sont les suivants :

- l'évaluation psychologique de l'IG ;
- l'exclusion des principales comorbidités qui pourraient interférer physiquement et psychologiquement avec la procédure de réassignation de genre ;
- l' expérience de vie en situation réelle (EVSR) au cours du traitement hormonal, à effectuer au cours de suivis psychologiques individuels ou de groupes jusqu'à redéfinition chirurgicale du genre, afin de répondre aux exigences juridiques et réglementaires qui régissent le changement de sexe dans chaque pays.

La majorité des sujets TIG sont des hommes biologiques qui souhaitent devenir femmes (MtF). Chez ces sujets, le traitement endocrinien sert l'objectif suivant : bloquer la production androgène et agir sur les cibles périphériques afin d'induire le développement progressif d'un phénotype féminin.

Le premier effet est obtenu par les oestrogènes et/ou les antiandrogènes « centraux » — tels que l'acétate de cyprotérone (CPA) et la spironolactone (SP) qui ont essentiellement des effets antigonadotrope, ainsi que par les antiandrogènes « périphériques », tels que l'azastéroïde et la flutamide, qui agissent au niveau des récepteurs.

Une minorité de sujets TIG sont des femmes biologiques qui souhaitent devenir hommes. Chez ces sujets, le TH est destiné à bloquer le cycle des menstruations et à induire une masculinisation phénotypique progressive. Ces deux aspects sont garantis par un traitement à la testostérone à des doses progressives.

Chez tous ces sujets, il est obligatoire d'effectuer des bilan biologiques sanguins, des analyses hormonales et génétiques ainsi qu'une exploration par ultrasons (seins chez les FtM et pelvien chez les MtF). Ces analyses doivent être effectuées en conditions basales et EVSR suivant les indications cliniques.

Après une gonadectomie chirurgicale, il se produit un hypogonadisme primaire qui doit être traité par une thérapie de substitution chronique. Le rôle essentiel de ce traitement doit être expliqué à toutes les personnes avant l'intervention chirurgicale, avec justification du suivi postchirurgical, un point qui est actuellement absent dans la littérature. En fait, on constate une rareté des données sur le traitement endocrinien ou le suivi en dehors de quelques publications sur les complications postchirurgicales ou l'activité sexuelle après transformation anatomique.

L'endocrinologue joue un rôle essentiel dans le conseil aux patients TIG. Son expertise sexologique et médicale est vitale pour les patients en demande d'aide au regard de leur état. Après une période tragique de réductionnisme psychoenvironnemental, au cours de laquelle on recommandait la psychanalyse et la psychothérapie en vue d'induire chez le patient une acceptation de son genre biologique, le traitement de choix d'un véritable TIG est désormais hormonal, chirurgical, avec redéfinition légale du genre. Même si une large majorité d'adultes avec TIG primaire ne peuvent ou ne veulent pas accepter leur genre biologique par le biais de la psychothérapie, une aide psychologique est presque toujours nécessaire au cours du long processus vers la mise en adéquation du corps, du rôle social et de la sexualité du patient avec son identité. L'endocrinologue, grâce à son rôle essentiel dans les TIG, doit combattre l'idée erronée selon laquelle les personnes qui souhaitent changer de genre sont des déviants sexuels.

Full English version

Introduction

Gender identity is dramatically influenced by hormones. Macro and micro-anatomical differences in the bed nucleus of the stria terminalis (BSTc) and its sex reversal in the transsexual brain clearly support the paradigm that in transsexuals sexual differentiation of the brain and genitals may go into opposite directions and point to a neurobiological basis of gender identity disorder (Kruijver et al., 2000). This agrees with the evidence that gender dysphoria begins relatively early in life (around five to six years-old).

The management of adult persons affected by Gender Identity Dysphoria (GID) involves endocrinologists who prescribe hormonal treatment (HT) aimed to modify physical aspect and match it with the gender identity (GI) these persons feel to belong to.

Many of these persons have already undergone cross-gender hormone self-administration, frequently at high dosages, while others start treatment for the first time. These differences should not influence the endocrinologist's approach, which must comply with specific guidelines. The latter are well defined in those countries where scientific societies and/or associations deal with and provide the entire medical treatment.

The universally accepted keypoints of GID treatment are:

- psychological assessment of GI;
- exclusion of major co-morbidities which could physically and psychologically interfere with the sex reassignment procedure;
- real life test (RLT)[1] during hormonal treatment, to be performed during individual or group psychological follow-up until surgical sex reassignment (SSR), in order to comply with specific laws that regulate sex change in each country (Guidelines for Transgender Care, 2006; Gooren et al., 2008)

In Italy Law 164/82 allows hormonal and surgical sex reassignment; generalities can be changed only by those subjects who have already modified their phenotype.

In 1998 the Italian National Observatory on Gender Identity (O.N.I.G.) proposed specific guidelines for cross-sex hormone treatment (www.onig.it), which are currently under revision.

Treatment protocols

In Italy HT can be prescribed by endocrinologists only after a well-defined diagnosis of GID has been formulated by trained psychologists/psychiatrists.

Prescriptions must be preceded by exclusion or preliminary and effective treatment of any concomitant pathological condition (diabetes, hypertension, obesity, etc.) or correction of smoking and drinking habits.

[1] According to proposals of WPATH Standards of Care (SOC) Revisions: Real Life Experience.

Table 1 Effects of hormone treatment.
Effets des traitements hormonaux.

MtF
Mammary gland growth
Partial fat mass redistribution
Modifications of skin and hair characteristics (thinner skin, reduced hair distribution at trunk, extremities, face, reduced balding)
Testis hypotrophy with hypo- or a-spermia, (reduced/supressed fertility [Sapino et al., 1987]), reduction/disappearance of erectile function (reduced libido)
FtM
Mild mammary gland hypotrophy
Fat mass redistribution
Body weight, muscle mass and strength increase
Increased face and body hair growth and increased balding
Clitoris hypertrophy, amenorrhea, infertility
Permanent voice deepening
Increased libido and aggressiveness (?)

RLT is finalized to improve the psychosocial functioning according to the desired sex and allows also to confirm the diagnosis.

Full explanation about the characteristics of HT is mandatory prior to start treatment, in order to obtain informed consent and the best compliance to treatment itself. It is very important to explain to the persons what reasonable changes they can obtain — as reported in Table 1 — and correlated risks (Godano, 1995).

Male to Female (MtF) Treatment

The majority of GID persons is represented by biological males who want to become women (MtF). In these subjects endocrine treatment has the following purposes: to block androgen production and action at peripheral targets and to induce the progressive development of a female phenotype.

The first effect is obtained through estrogens and/or ''central'' antiandrogens like cyproterone acetate (CPA) and spironolactone (SP), which have mainly antigonadotrophic effects, and through ''peripheral'' antiandrogens, like azasteroids and flutamide, which act at the receptor level.

Estrogens. Phenotype feminization is initiated and guaranteed by estrogen administration that is currently performed with oral or transdermal 17-beta-estradiol preparations (Gooren et al., 2008). Doses necessary to feminize a biological male are on average higher than those used for female replacement therapy (2—4 mg/day orally or two or more gel dosages/day). Parenteral estrogen preparations are well accepted to improve clinical effects (Guidelines for Transgender Care, 2006), but these formulations are not available any more in Italy.

One of the most important desired estrogen effects is mammary gland growth which usually starts with estrogen/central antiandrogen-progestative association in a few months and is completed in two years with acinar and lobular formation (Godano et al., 1990; Kanhai et al., 2000; Guidelines for Transgender Care, 2006).

The entity of mammary gland development varies more according to genetically defined peripheral sensitivity than to the dosage and characteristics of prescribed hormonal substances. Interestingly, there is neither clinical nor mammographic objective parameter to define the appropriateness of glandular development in each specific subject.

More than 60% of MtF develops hyatrogenic hyperprolactinemia, sometimes with galactorrhea, which may be treated with dopaminergic drugs, if requested; prolactinomas are very rare.

Occasionally MtF on oral estrogens develop colelythiasis, which requires a temporary discontinuation of hormonal treatment and surgical intervention (Becerra Fernández et al., 1999).

The most hazardous complication of HT in MtF in the past years was thromboembolism. Nowadays this complication is far less frequent since MtF GID persons at risk, mainly over 40 years of age, are treated with trans-dermal estradiol (Asscheman et al., 1989; van Kesteren et al., 1997; Toorians et al., 2003; Gooren et al., 2008).

Antiandrogens. Antiandrogens complete and enhance estrogen effects on feminization.

CPA and SP are the most commonly used medications: they possess central but also peripheral effects at the receptor level and are prescribed at dosages of 50—200 mg/day and 25—200 mg/day, respectively. Moreover, CPA exerts also a progestative effect, which is very useful to stimulate the histological change and development of the mammary gland. Similarly SP induces gynecomastia due to its antiandrogenic, progestative and estrogen-like effects.

Azasteroids are prescribed at a dosage of 5 mg/day (finasteride) or 0.5 mg/day (dutasteride) and 125—250 mg/day (flutamide) in order to improve the desired effects at skin/hair level.

GnRH analogues. Only in case of serious side effects during antiandrogen treatment (mainly with CPA), especially in persons with relative contraindications to estrogens, it is reasonable to use GnRH analogues to block the hypothalamus-pituitary-testicular axis in association with low doses of estrogens (Dittrich et al., 2005).

The routine use of GnRH analogues is not justified in adults in terms of cost-effectiveness. The unique real reason for not using castration by GnRH agonists is the cost. Side effects of the whole treatment (GnRH + oestrogens) are in fact much lower than any other treatment.

Progestins. Progestin administration is controversial because of potential adverse effects (depression, metabolic changes, etc). Progestins might be required only in patients who do not tolerate an estrogen-based regimen.

Female to Male (FtM) Treatment

A minority of GID persons is represented by biological females who want to become men. In these subjects the HT is aimed to block menstrual cycles and to induce a progressive phenotype masculinization. Both these aspects are guaranteed by testosterone treatment at progressive doses (T enanthate 100—250 mg/week intra-muscular [IM]) or 50—100 mg/day transdermal administration (Gooren et al., 2008). Intra-muscular regimen is preferable (Guidelines for Transgender Care, 2006) and the most recent long-acting preparation (T undecanoate 1000 mg/12 weeks) seems to be very promising and appreciated for its comfort of use (Mueller et al., 2007).

Gel preparations are not so well tolerated due to several reasons such as reduced cutaneous absorption, frequent skin reactions and possible menstrual bleeding. Along with the desired androgenic effects, seborrhoea and acne frequently occur sometimes requiring a low-dose peripheral antiandrogen treatment. In this case, no interference with final treatment outcome is recorded (personal data).

Both in MtF and in FtM persons it is mandatory to perform general blood chemistry, hormonal, and genetic evaluations and ultrasound assessment as reported in Table 2. These evaluations must be performed basally and during RLT according to clinical indications.

Treatments may be modified on the basis of the evaluations reported in Table 2 and according to clinical conditions.

It is still matter of debate whether and how to maintain hormone administration for those persons who do not wish to undergo surgical sex reassignment but want to maintain the newly acquired sexual characteristics.

It is not advisable to leave these persons to a cross-gender hormone self-administration but it would be better to follow them up in order to obtain a good experience in long-term treatment with cross sex hormones and to provide a good standard of health.

Table 2 Evaluations for hormone treatments.
Évaluations en vue du traitement hormonal.

Basally
Blood chemistry
blood count, glucose, creatinine, total cholesterol, HDL cholesterol, triglycerides, CRP, liver enzymes, bilirubine, urine analysis.
Hormones (MtF and FtM):
FSH, LH, Total testosterone, PRL, TSH, insulin, SHBG
Within six days from menstrual bleeding in FtM: 17βE2,17αOHP
Radiologic exams
according to clinical conditions
Genetic tests
cariotype (in case of SSR)
In MtF only the following exams are advisable
Factor V mutations (G1691A—H1299 [R2]) (*if genetic tests are not feasible check APC Resistence*)
C and S Proteins
Prothrombin G 20210A mutations
A.T. III
DURING RLT (every 3-4 months)
Blood chemistry
blood count, glucose, creatinine, total cholesterol, HDL cholesterol, triglycerides, CRP, liver enzymes, bilirubine, urine analysis.
Hormones
(MtF): LH, Total testosterone, 17 ß E2, PRL, (TSH, insulin)
(FtM): LH,17βE2, total testosterone, PRL, (TSH, insulin)
Mammary ultrasound in MtF when clinically appropriate.
Pelvic ultrasound in FtM when presurgical testosterone treatment exceeds two years.

Persons who have to undergo surgical treatments have to stop CPA and oral estradiol one month in advance, trans-dermal estradiol 15 days before, while peripheral antiandrogens and SP may be taken until hospital admission. Immobilization is a thrombogenic risk factor and sex steroids may aggravate the risk of thromboembolism. Once subjects are fully mobilized again, hormone therapy may be reinstated. This applies also to testosterone in FtM where it is suggested to suspend IM testosterone one month before surgery and to suspend transdermal testosterone two weeks before surgery. This approach avoids symptoms of hormone withdrawal (e.g. uterine bleeding, erections, etc.), which are poorly tolerated by persons at the end of their cross-sex treatment.

Postsurgical hypogonadism: the essential role of endocrine treatment

Following surgical gonadectomy, primary hypogonadism occurs and must be treated with chronic replacement therapy. The essential role of this treatment has to be clarified to all persons prior to surgical intervention, thus explaining the necessity of postsurgical follow-up, which is currently absent in a significant manner in literature. In fact, along with few publications about postsurgical complications or sexual activity after anatomical transformation, data about endocrine treatment or follow-up are extremely scarce (Lobato et al., 2006; Gooren et al., 2008).

Male to Female (MtF)

Estradiol replacement with oral estrogens, or trans-dermal preparations immediately postoperative and later in life, are strongly recommended in all these subjects in order to maintain quality of life, which is the target of medical management for GID persons. Doses required to obtain a correct substitution must guarantee circulating levels corresponding to those of age and sex-matched individuals.

Only a physiological sexual hormonal milieu is able to guarantee a correct bone, glucose, lipid and protein metabolism, central neurotransmission and general well-being.

For instance, it is well known from the literature that GID persons under estrogen treatment do not develop osteoporosis. Anyway, according to specific situations, MOC DEXA is useful.

MtF follow-up includes also blood chemistry, hormone assessment yearly, and mammographic and ultrasound mammary examinations as well, even though nowadays there are no data about a significant oncologic risk in this kind of persons. However, they cannot be correctly compared, on an epidemiological basis, neither with biologic males nor with biologic females. On the other hand, ultrasound prostate morphology evaluation seems not to be indicated other than in presence of urinary obstructive symptoms. Similarly, PSA evaluation is not usually indicated, since up to now there are no reports of an increased oncologic risk (Gooren et al., 2008).

Female to Male (FtM)

Testosterone replacement, preferably with i.m. long-acting preparations, is strongly recommended in all these subjects in order to maintain quality of life, which is the target of medical management for GID persons. Doses required to obtain a correct substitution must guarantee circulating levels corresponding to those of age and sex-matched individuals.

Also, for male gender, a physiological sexual hormonal milieu is necessary to guarantee a correct bone, glucose, lipid and protein metabolism, central neurotransmission and general well-being.

In FtM, the possible impairment of bone metabolism after ovariectomy not withstanding a correct androgen replacement is currently under investigation (van Kesteren et al., 1998; Mueller et al., 2005).

FtM follow-up includes also blood chemistry, yearly hormone assessment, and periodic mammographic assessment only when a mammary gland residue is present.

Post GRC surgery

Suspend CPA and systemic estrogens at least one month before surgery and suspend transdermal estrogens and peripheral antiandrogens one to two weeks before any surgery. Since immobilization is a thrombogenic risk factor and sex steroids may aggravate the risk of thromboembolism, this suspension should be performed before any important surgery requiring a long postoperative period. Once subjects are fully mobilized again, hormone therapy may be reinstated. For FtM it is suggested to suspend i.m. testosterone one month before surgery and to suspend transdermal testosterone two weeks before surgery.

The role of counselling

The endocrinologist plays a pivotal role in GID counselling (Jannini et al., 2006). His sexological and medical expertise is essential for patients seeking help for this condition. After a tragic period of psycho-environmental reductionism, when psychoanalysis and psychotherapy were recommended in the attempt to induce the patient to accept his/her biological gender (Meyer, 1979), the treatment of choice for true GID is now hormonal, surgical, and legal gender reassignment. However, differential diagnosis, although not easy, is essential before any treatment to distinguish between true (''primary'') GID (where the patient sexually and generally thinks of him/herself as a member of the opposite sex) and the ''secondary'' form, paraphilic behaviour (transvestic fetishism and autogynephilia) where the subject is sexually aroused by cross-dressing and acting as a member of the opposite sex. Most of these cases require psychiatric aid, also for the reason that major psychiatric disturbances must be excluded before hormonal therapy. Even if the large majority of adults with primary gender dysphoria cannot, or will not accept their given biological gender through use of psychotherapy, supportive psychological help is almost always needed during the long journey to match the patient's body, social role, and sexuality to his/her identity (Brown, 1990).

Transsexuals often form support groups, magazines, newsletters, websites, forums and chat rooms: many of them are well informed and share information, but have a constant desire to be personally counselled and guided. The endocrinologist should be able to counsel on dangerous

behaviours (alcohol, drugs, prostitution) with a humanistic perspective, supporting the patient's empowerment of self-identification. Furthermore, the endocrinologist, expert in sexual medicine, should educate family, relatives, and friends about the patient's condition, also influencing public opinion where possible. Prejudices, homophobia, and morbidness are still widely present even in the most civilized societies. The endocrinologist, in force of its pivotal role in GID, should fight against the common misconception that people who want to change sex are sexual deviants.

Conclusions

In consideration of scanty literature data about long-term follow-up, we can conclude that a good quality of life may be reached by persons who underwent a correct RLT and developed a good self-consciousness during transformation, who were assisted by a medical and psychological trained and integrated team, and who had a good social and family environment (Godano et al., Gender dysphoria: clinical, sociocultural and psychosexual data of 134 patients. XIV HBIGDA Symposium, Kloster Irsee, 7—10 september 1995).

HT prescribed by experienced endocrinologists who know both pharmacological preparations and their biological effects in transgender persons, do not show significant adverse effects. In fact, up to now there are no reports of increased morbidity or mortality in persons treated with cross-sex hormones (Gooren et al., 2008).

References

Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism 1989;38:869—73.

Becerra Fernández A, de Luis Román DA, Piédrola Maroto G. Morbidity in transsexual patients with cross-gender hormone self-treatment. Med Clin (Barc) 1999;113:484—7.

Brown GR. A review of clinical approaches to gender dysphoria. J Clin Psychiatry 1990;51:57—64.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. Exp Clin Endocrinol Diabetes 2005;113:586—92.

Godano A, Massara D, Grassi G, Genovese MG, Cavallotti GP, Bocchini R. Male transsexualism and hormonal therapy: radiologic pictures of the breast. Arch Ital Urol Nefrol Androl 1990;62:107—11.

Godano A. Terapia medica nel transessualismo. G Ital Androl 1995;2:160—4.

Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 2008;93:19—25.

Guidelines for Transgender Care. Int J Transgenderism 2006; 9(3/4):1—231.

Jannini EA, Lenzi A, Wagner G. Behavioural Therapy and Counselling. In: Schill WB, Comhaire FH, Hargreave TB, editors. Andrology for the Clinician. Berlin: Springer; 2006. p. 598—607.

Kanhai RC, Hage JJ, van Diest PJ, Bloemena E, Mulder JW. Short-term and long-term histologic effects of castration and estrogen treatment on breast tissue of 14 male-to-female transsexuals in comparison with two chemically castrated men. Am J Surg Pathol 2000;24:74—80.

Kruijver FPM, Zhou J-N, Pool CW, Hofman MA, Gooren LJG, Swaab DF. Male-to-female transsexuals have female neuron numbers in a limbic nucleus. J Clin Endocrinol Metab 2000;85: 2034—41.

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, et al. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. Arch Sex Behav 2006;35:711—5.

Meyer JM. The theory of gender identity disorders. J Am Psychoanalytic Assoc 1979;30:381—418.

Mueller A, Dittrich R, Binder H, Kuehnel W, Maltaris T, Hoffmann I, et al. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. Eur J Endocrinol 2005;153:107—13.

Mueller A, Kiesewetter F, Binder H, Beckmann MW, Dittrich R. Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. J Clin Endocrinol Metab 2007;92:3470—5.

Sapino A, Pagani A, Godano A, Bussolati G. Effects of estrogens on the testis of transsexuals: a pathological and immunocytochemical study. Virchows Arch A Pathol Anat Histopathol 1987;411:409—14.

Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 2003;88:5723—9.

van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997;47:337—42.

van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. Clin Endocrinol (Oxf) 1998;48:347—54.